Letter: Inorganic Nitrite Selectively Dilates Epicardial Coronary Arteries

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Inorganic nitrite (NO_2^-), as sodium nitrite, or derived from dietary nitrate found in green leafy vegetables and beetroot, has potential as a tolerance-free therapy in Heart Failure with Preserved Ejection Fraction (HFpEF)(1) including pulmonary hypertension-associated HFpEF (PH-HFpEF) (2). Nitrite affects small and large arteries and veins. Previous studies demonstrated hypoxia (versus normoxia) enhanced nitrite-induced dilatation by 30-50% in small resistance arterioles, but not veins (since venous blood is already desaturated) (3). We recently demonstrated that nitrite selectively dilates peripheral conduit arteries in a normoxia-dependent/hypoxia-inhibited manner, and selectively lowers aortic blood pressure (afterload)(4). We confirmed this latter effect with 6 months' dietary nitrate (beetroot juice) in 126 patients(5). Nitrite has similar selectivity as nitroglycerin (GTN) for conduit, versus small resistance arterioles(4). We therefore investigated whether nitrite also selectively vasodilates epicardial coronary (conduit) arteries.

Following institutional and ethical approvals and informed consent, we recruited patients undergoing diagnostic coronary angiography, including those with an angiographically-normal coronary artery/without previous coronary intervention.

A 0.014-inch coronary Doppler wire (Flow Wire, Phillips Volcano, USA) was positioned within the proximal artery and average peak velocity (APV) measured following five-minute infusions of 0.9% saline (baseline), low-dose sodium nitrite (2.6μmol/min), high-dose sodium nitrite (26μmol/min), and GTN (1μg/min). Angiographic images were obtained simultaneously. Quantitative Coronary Analysis (QCA) was performed off-line with measurements of vessel diameter (d) in the 5mm segment distal to the tip of the Doppler wire. Coronary blood flow (CBF, cm^3/s) was calculated by: CBF= (APV/2) x cross-

sectional area. Coronary resistance (mmHg/cm^3/s) was calculated as mean arterial pressure divided by coronary blood flow.

Nine patients (mean age 56 years, 5 male, 78% hypertensive) received both doses of nitrite, and GTN, and had angiographic and Doppler flow traces of sufficient quality to be included in the analysis. The higher dose of nitrite (26μmol/min) and GTN both significantly dilated the coronary artery compared to baseline: diameter-change (mean [95% CI]): +8.9% [+2.0,+15.8], p=0.01 and +10.8% [+1.0,+20.5] p=0.03, respectively (**Figure 1A**); with no significance difference between nitrite and GTN (p=0.45). Lower dose nitrite (2.6μmol/min) had no significant effect (+3.9% [-2.8,+10.6], p=0.3).

GTN increased coronary flow relative to baseline (median [interquartile range]): +23.9% [+6.3,+72.7], p=0.02. Nitrite (2.6μmol/min and 26μmol/min) lacked significant effect on coronary flow: +12.0% [-10.2, +24.1] p>0.99 and +16.9% [+3.2, +64.4] p>0.99 respectively. This was despite relatively high estimated intracoronary nitrite concentrations 73.7 [57.8, 154.9] microM(median [IQR]) for nitrite (2.6μmol/min) and 705 [555, 1179]microM (median [IQR]) for nitrite (26μmol/min).

GTN also lowered coronary resistance relative to baseline (mean [95% CI]): -29.3% [-52.8,-5.9] p=0.02, and versus nitrite (26μmol/min): -10.4% [-18.3,-2.4] p=0.01. By contrast, nitrite (2.6μmol/min and 26μmol/min) had no significant effect on coronary resistance: -11.1% [-36.7,+14.5] p=0.52, and -19.0% [-43.4,+5.4] p=0.13, respectively (**Figure 1B**).

There were no significant overall differences in central systolic, diastolic, or mean blood pressure with any of the interventions versus baseline. Heart rate changed -3.1 bpm [-0.2,-6.1], p=0.02, with nitrite (2.6μmol/min), but not with nitrite (26μmol/min) or GTN.

In summary, this is the first data to show that inorganic nitrite dilates epicardial coronary arteries; moreover, this was selective (and dose-dependent). Whilst the results should be interpreted with caution, given the small sample size, the indirect measures of coronary flow, and the trend towards a change in coronary flow/resistance, they support our findings in the peripheral circulation(4) of nitrite's physiological action as a normoxia-dependent selective conduit artery dilator over resistance arteries, even in the metabolically-active myocardium. These findings also have important implications for our understanding of the potential beneficial cardiovascular properties of nitrite derived from dietary nitrate sources such as beetroot and green leafy vegetables: nitrite acts principally on large, rather than small vessels in the heart.

Figure List

Figure 1. Percentage change in: **A** coronary artery diameter, and **B** coronary resistance. Nitrite (2.6) and Nitrite (26) denote nitrite (2.6 μmol/min) and nitrite (26 μmol/min), respectively. Data shown as Mean±SEM. Significance shown as *p<0.05 vs baseline, †p<0.05 vs nitrite (2.6 μmol/min), ‡p<0.05 vs nitrite (26 μmol/min)

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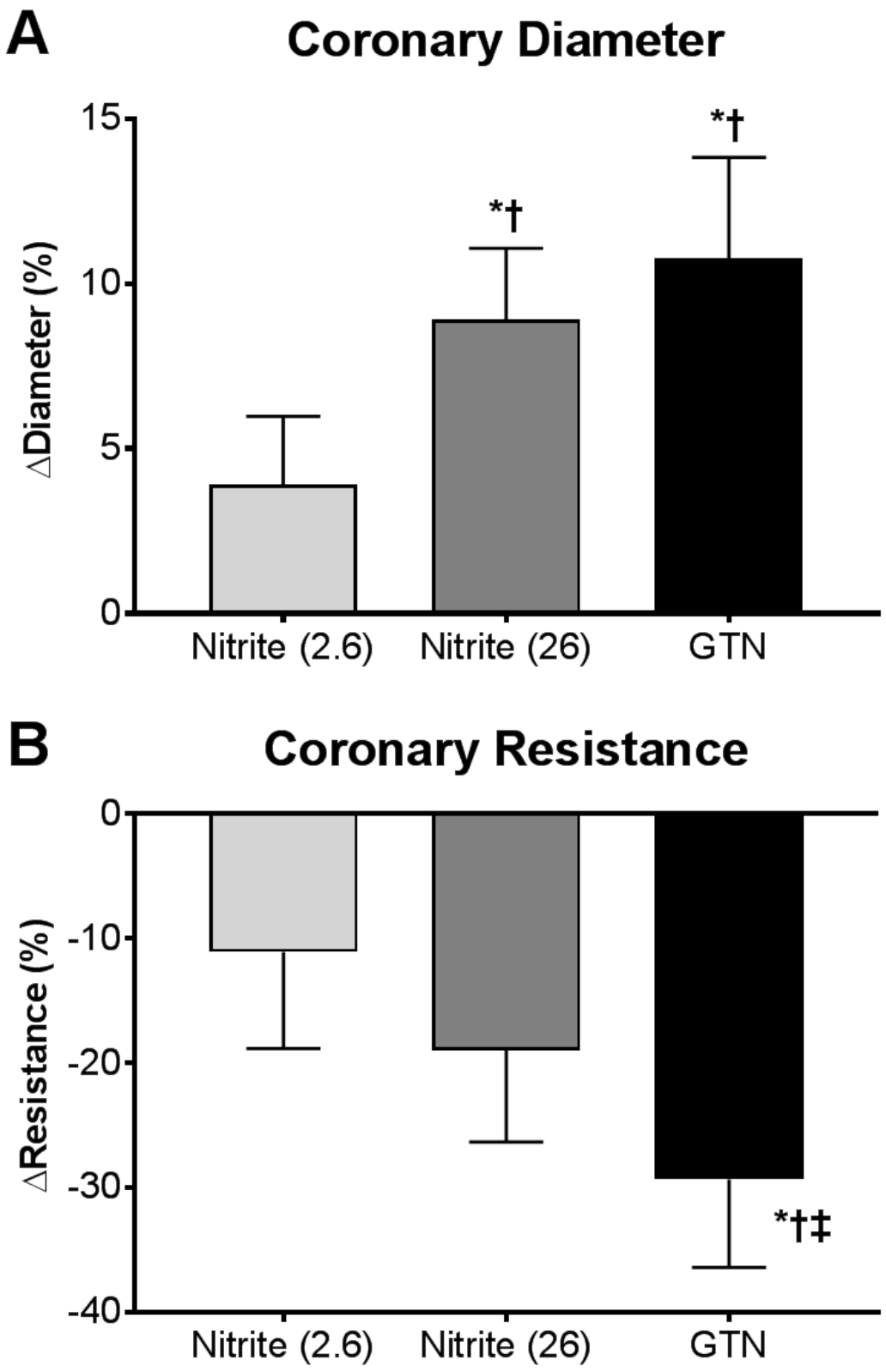
A
Coronary Diameter
15
10
5
0
ΔDiameter (%)
*†
*†
Nitrite (2.6)
Nitrite (26)
GTN
B
Coronary Resistance
0
-10
-20
-30
-40
ΔResistance (%)
*†‡
Nitrite (2.6)
Nitrite (26)
GTN